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Research Note

Metabolomic Biomarkers in Amniotic Fluid for Early Diagnosis of Preterm Birth and Fetal Growth Restriction

Charalampos Kolvatzis[1], Konstantinos Tsiantas[2], Ioannis Tsakiridis[1], Paris Christodoulou[2], Antigoni Cheilari[3], Ioannis Kalogiannidis[1], Panagiotis Zoumpoulakis[2], Apostolos Athanasiadis[1]

[1] *Third Department of Obstetrics and Gynecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece*

[2] *Department of Food Science and Technology, University of West Attica, Athens, Greece*

[3] *Department of Pharmacognosy and Natural Products Chemistry, Faculty of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece*

Corresponding author: Charalampos Kolvatzis, Third Department of Obstetrics and Gynecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece; Email: charis_kolv@hotmail.com

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Abstract

Preterm birth, affecting about 10% of pregnancies, significantly contributes to perinatal morbidity and mortality. Recent research indicates that metabolomics could enhance pregnancy outcomes and reduce costs by identifying biomarkers related to common pregnancy complications. Our team focused on analyzing amniotic fluid collected during the second trimester to identify potential biomarkers for preterm birth using 1H-NMR metabolomic analysis. We compared amniotic fluid samples from women who delivered prematurely with those who delivered at term. Multivariate principal component analysis revealed dimethylglycine, glucose, myo-inositol, and succinic acid as potential biomarkers for preterm birth prognosis and early diagnosis. Further analysis demonstrated distinct regulation patterns of these metabolites in relation to fetal growth centiles. For instance, dimethylglycine and glucose were upregulated in fetuses above the 20th centile, while citrate and succinate were upregulated in those below it. With Area Under the Curve (AUROC) values over 0.75 and p-values less than 0.05, these metabolites show promise as reliable biomarkers for predicting fetal growth restriction. This approach could significantly impact maternal-fetal medicine by facilitating early diagnosis and personalized interventions. Future research should focus on validating these findings in larger populations and exploring the underlying mechanisms of metabolite regulation.

Keywords

amniotic fluid, preterm delivery, NMR metabolomics, multivariate analysis

Preterm birth is a major contributor of perinatal morbidity and mortality, complicating about one out of ten pregnancies.[1] Several studies of metabolomics are currently available regarding common complications of pregnancy; their use could improve pregnancy outcomes and lead to cost reduction.[2-4]

Recently, our team investigated whether the analysis of the metabolic composition of amniotic fluid collected from pregnant women in the second trimester could provide valuable information on preterm birth. We used 1H-NMR metabolomic analysis to examine amniotic fluid samples from women who delivered prematurely and those who delivered at term. Using multivariate principal component analysis, dimethylglycine, glucose, myo-inositol and succinic acid were identified as potential biomarkers for the prognosis and early diagnosis of preterm birth.[5]

Following further analyses, utilizing the same methodology[5], we found that the previously identified metabo-

lites show distinct patterns of regulation that correlate with specific pregnancy milestones. This means that the levels of these metabolites change predictably, according to the fetal growth centile. For example, according to **Fig. 1**, dimethylglycine and glucose are upregulated in fetuses >20 centile, while citrate and succinate are upregulated in those <20 centile. Based on the fact that these metabolites are validated (Area Under the Curve, AUROC >0.75 and p-value <0.05), this regulation pattern suggests that the above metabolites could be used as reliable biomarkers to predict fetal growth restriction. This may have a significant impact in maternal-fetal medicine since accurate prediction of birthweight could favor early diagnosis of implications related to prenatal monitoring, allowing personalized and timely interventions to ensure the health and safety of the fetus/neonate.

Herein, by combining NMR metabolomics and a unique multivariate statistical approach, we provided new insights into amniotic fluid biomarker discovery anhighlighted the potential for metabolomics to contribute to improving maternal and neonatal outcomes. Future studies should aim to validate these biomarkers in larger and more diverse

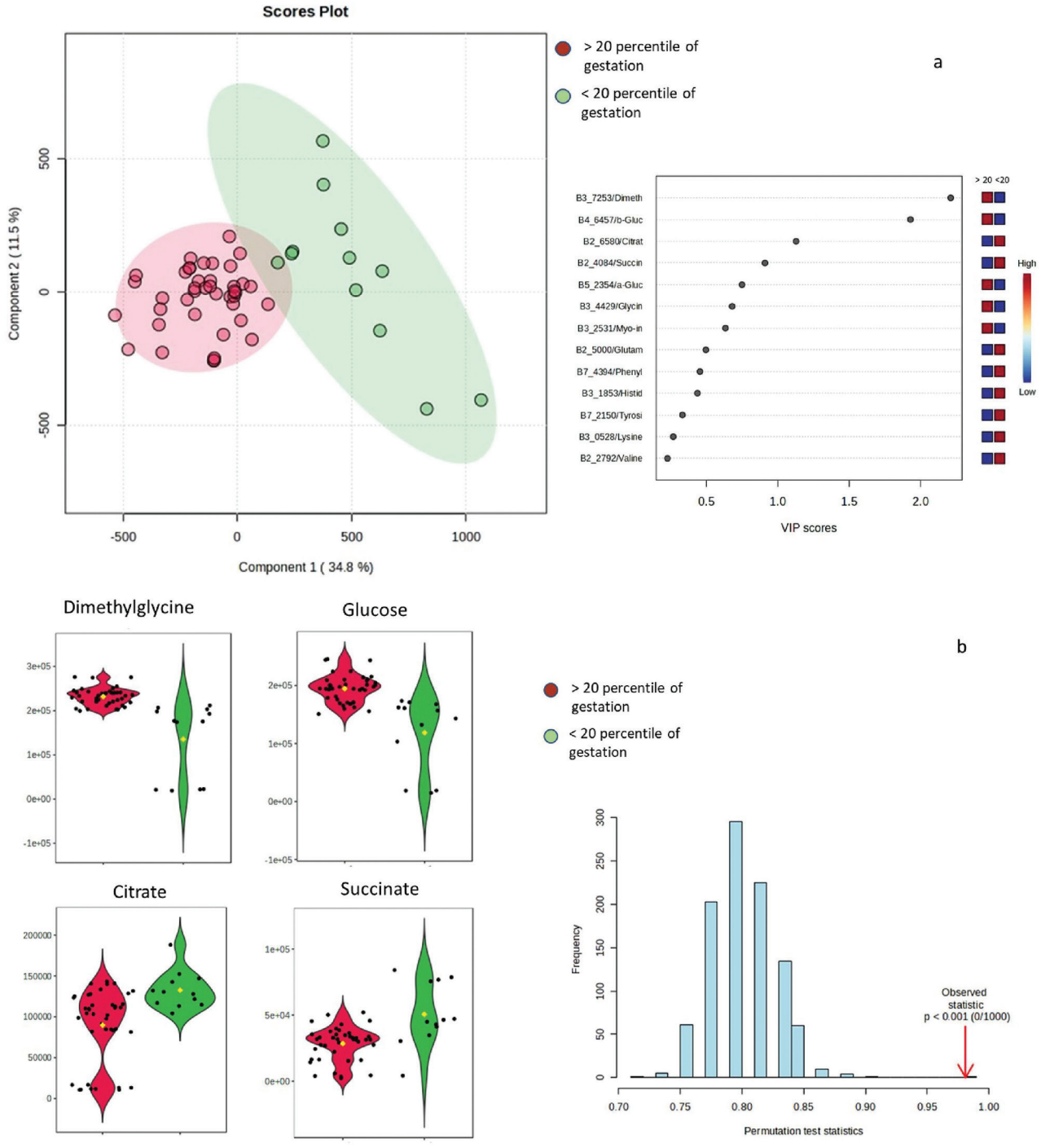

Figure 1. Metabolites of interest derived by discriminant analysis of fetal growth centile.

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populations and investigate the mechanisms driving these regulatory changes.

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Competing Interests

The authors have declared that no competing interests exist.

Author contributions

Conceptualization: A.A., I.K., P.Z., C.K., and P.C.; methodology: P.C., I.T., K.T., A.C., P.Z., A.A., and C.K.; software: P.C., K.T., and A.C.; investigation: C.K., I.T., K.T., and P.C.; data curation: C.K., P.C., K.T., and A.C.; resources: P.Z., A.A., and C.K.; visualization: P.C.; writing original draft preparation: C.K., I.T., P.C., K.T., and A.C.; writing review and editing: C.K., I.T., P.C., K.T., N.S.T., A.A., and I.K.; supervision: A.A., I.K., and P.Z.; project administration: P.Z. and A.A. All authors have read and agreed to the published version of the manuscript.

Ethical statement

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Aristotle University of Thessaloniki Research Ethics Committee (Prot. No. 1.662/21 November 2018) for studies involving humans. Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Метаболомные биомаркеры в амниотической жидкости для ранней диагностики преждевременных родов и задержки роста плода

Харалампос Колвацис[1], Константинос Циантас[2], Йоанис Цакиридис[1], Парис Христодулу[2], Антигони Чейлари[3], Йоанис Калогианидис[1], Панайотис Зумпулакис[2], Апостолос Атанасиадис[1]

[1] *Третья кафедра акушерства и гинекологии, Факультет медицины, Институт медицинских наук, Университет имени Аристотеля, Салоники, Греция*

[2] *Кафедра пищевых наук и технологий, Университет Западной Аттики, Афины, Греция*

[3] *Кафедра фармакогнозии и химии натуральных продуктов, Факультет фармации, Национальный Афинский университет имени Каподистрии, Афины, Греция*

Адрес для корреспондецнии: Харалампос Колвацис, Третья кафедра акушерства и гинекологии, Факультет медицины, Институт медицинских наук, Университет имени Аристотеля, Салоники, Греция; E-mail: charis_kolv@hotmail.com

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Резюме

Преждевременные роды, затрагивающие около 10% беременностей, вносят значительный вклад в перинатальную заболеваемость и смертность. Недавние исследования показывают, что метаболомика может улучшить исходы беременности и снизить расходы за счёт выявления биомаркеров, связанных с распространёнными осложнениями беременности. Наша команда сосредоточилась на анализе амниотической жидкости, собранной во втором триместре, для выявления потенциальных биомаркеров преждевременных родов с использованием метаболомного анализа 1H-ЯМР. Мы сравнили образцы амниотической жидкости у женщин, родивших преждевременно, с теми, кто родил в срок. Многомерный главный компонентный анализ выявил диметилглицин, глюкозу, мио-инозитол и янтарную кислоту в качестве потенциальных биомаркеров для прогноза преждевременных родов и ранней диагностики. Дальнейший анализ продемонстрировал различные закономерности регуляции этих метаболитов в зависимости от процентилей роста плода. Например, диметилглицин и глюкоза были повышены у плодов выше 20-го процентиля, в то время как цитрат и сукцинат были повышены у плодов ниже него. При значениях Area Under the Curve (AUROC) более 0.75 и *p*-значениях менее 0.05 эти метаболиты обещают быть надёжными биомаркерами для прогнозирования ограничения роста плода. Этот подход может существенно повлиять на медицину матери и плода, способствуя ранней диагностике и персонализированным вмешательствам. Будущие исследования должны быть сосредоточены на подтверждении этих результатов в более крупных популяциях и изучении базовых механизмов регуляции метаболитов.

Ключевые слова

амниотическая жидкость, преждевременные роды, ЯМР-метаболомика, многофакторный анализ